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Pulse pressure and isolated systolic hypertension: Association with microalbuminuria

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Background. The long-term risk of end-stage renal disease is high in persons with isolated systolic hypertension, that is, those with an elevation of pulse pressure and not of diastolic pressure. Other data suggest that pulse pressure is a predictor of the hypertension-induced organ damage. Microalbuminuria is considered an early sign of glomerular damage caused by hypertension. The study shows the relationship of pulse pressure and isolated systolic hypertension to microalbuminuria in nondiabetic subjects.

Methods. This is a cross sectional analysis for a population sample of 677 men and 890 women, aged 45 to 64 years, who were without diabetes mellitus and macroalbuminuria. Data collection included: overnight urinary albumin and creatinine excretion; fasting plasma glucose, cholesterol, and creatinine; creatinine clearance; and blood pressure, weight, height, medical history, and smoking habit. Pulse pressure was calculated as systolic minus diastolic pressure. Isolated systolic hypertension was defined as systolic pressure $\geq$140 mm Hg in persons not on antihypertensive drugs and with diastolic pressure $<$90 mm Hg. Microalbuminuria was defined as urinary albumin excretion $\geq$20 μg/min.

Results. Pulse pressure and isolated systolic hypertension were significantly related to urinary albumin excretion and the prevalence of microalbuminuria in univariate and multivariate analyses. Controlling for gender and other variables, the risk of microalbuminuria was 1.71 with a 15 mm Hg higher pulse pressure (95% CI, 1.31 to 2.22) and 4.95 in the presence of isolated systolic hypertension (95% CI, 3.15 to 7.76).

Conclusions. In nondiabetic, middle-aged adults, pulse pressure and isolated systolic hypertension are directly related to microalbuminuria, independent of diastolic pressure and other correlates.

Key words: blood pressure, albuminuria, Gubbio Population Study, diastolic pressure, end-stage renal disease, risk factors for ESRD.

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End-stage renal disease is a mounting public health problem of great potential importance for medical care and prevention [1]. Hypertension is a risk factor for end-stage renal disease [2, 3]. The risk of end-stage renal disease also is high in persons with isolated systolic hypertension, that is, those with diastolic pressure in the nonhypertensive range and with an elevation only in pulse pressure, hence in systolic pressure [3].

The term microalbuminuria is defined as a moderate elevation in urinary albumin excretion that is considered to be an early sign of glomerular damage; it is a risk factor for end-stage renal disease in people with diabetes mellitus and a possible index of vascular damage in nondiabetics [4, 5]. In both diabetic and nondiabetic persons, high blood pressure is considered a determinant of the onset of microalbuminuria [5]. In alignment with this view, blood pressure reduction by antihypertensive drugs lowers urinary albumin excretion and favors the control of microalbuminuria [6, 7].

The idea of a continuous and graded relationship of blood pressure to the onset and progression of renal damage from the early to its ultimate stages may be supported by an association between blood pressure and microalbuminuria. Such an association has been consistently found in studies on hypertensive patients [8, 9], but not in epidemiologic studies [10–12]. More recently, a strong relationship of systolic and diastolic pressures to microalbuminuria was reported by an epidemiologic study based on the use of urine ultrafiltration [13]. For years, diastolic pressure has been considered a more important measurement than systolic pressure for the development of the organ damage secondary to hypertension [14, 15]. Recent data suggest that pulse pressure and isolated systolic hypertension could be greater risk factors than diastolic pressure [16–18]. The present epidemiologic study in nondiabetic adults reports data on the association of pulse

pressure and isolated systolic hypertension with microalbuminuria independent of other traits related to these variables.

METHODS

The Gubbio Population Study is an ongoing epidemiologic investigation in the hill town of Gubbio, located in central Italy [19–25]. The cohort for the present analysis, described in a previous article [13], consisted of persons aged 45 to 64 years who were without macroalbuminuria (defined as an overnight urinary albumin excretion <200 μg/min), with a fasting plasma glucose <7.8 mmol/L (140 mg/dL), were not on any treatment with insulin or antidiabetic drugs, and had no previous diagnosis of diabetes mellitus. Data collection included: antihypertensive treatment status; systolic and diastolic pressures; smoking habit; body mass index and body surface area; urinary excretion rate of creatinine and albumin in a timed overnight collection; and plasma glucose, cholesterol, and creatinine values. Laboratory procedures are described in a previous article [13]. Urinary albumin was measured by immunoturbidimetry; urinary samples were concentrated by ultrafiltration when the albumin concentration was <7 μg/mL.

Pulse pressure was calculated as systolic pressure minus diastolic pressure; mean pressure was defined as diastolic pressure plus one third of the pulse pressure. Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg and/or antihypertensive drug treatment. Isolated systolic hypertension was defined as systolic pressure ≥140 mm Hg in subjects not on antihypertensive drug treatment (untreated) and with a diastolic pressure <90 mm Hg. Within the group on antihypertensive drug treatment (treated), controlled hypertension was defined as systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg. Urinary albumin excretion was expressed as μg/min, and microalbuminuria was defined as urinary albumin excretion ≥20 μg/min. Urinary albumin concentration and urinary albumin/creatinine ratio were not used in analysis, since the definition of microalbuminuria on the basis of these indices is biased by the confounding influence of urine flow rate and creatininuria [13, 26, 27]. Creatinine clearance per 1.73 m^2 of body surface area was used as an index of the glomerular filtration rate.

The urinary albumin excretion value was logarithm transformed in linear regression analyses because it was positively skewed [13, 26]. To combine the smoker and nonsmoker data in an analysis, the reported number of cigarettes per day was logarithm-transformed as previously described [13, 24, 25]. Statistical procedures included simple correlation analysis, analysis of variance (ANOVA), and chi-square analysis with tests for linearity, univariate and multivariate linear and logistic regression analyses. Relative risks and 95% confidence intervals were calculated with exponentiation of logistic regression coefficients and standard error (SE).

Table 1. Descriptive statistics for blood pressure and other variables: mean ± SD or prevalence

	Men	Women
Number of persons	677	890
Systolic pressure *mm Hg*	129.4 ± 17.9	129.8 ± 18.1
Diastolic pressure *mm Hg*	79.0 ± 9.7	78.1 ± 9.5
Pulse pressure *mm Hg*	50.4 ± 13.7	51.8 ± 13.3
Mean pressure *mm Hg*	95.7 ± 11.2	95.4 ± 11.5
On antihypertensive drug treatment *N* (%)	113 (16.7%)	163 (18.3%)
On antihypertensive drug treatment and controlled[a] *N* (%)	70 (10.3%)	76 (8.5%)
Untreated[b] and with isolated systolic hypertension[c] *N* (%)	75 (11.1%)	97 (10.9%)
Untreated[b] and with diastolic pressure ≥90 mm Hg, *N* (%)	75 (11.1%)	84 (9.4%)
Urinary albumin excretion *μg/min*	10.4 ± 10.1	8.9 ± 8.5
Logarithm-transformed *μg/min*	0.893 ± 0.327	0.846 ± 0.304
With microalbuminuria[d] *N* (%)	38 (5.6%)	21 (2.4%)
Creatinine clearance, mL/min × 1.73 m^2 of body surface area	94.5 ± 23.0	89.1 ± 20.5

[a] With systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg
[b] Not on antihypertensive drug treatment
[c] With systolic pressure ≥140 mm Hg and diastolic pressure <90 mm Hg
[d] Urinary albumin excretion 20–199 μg/min

RESULTS

Descriptive statistics

Descriptive statistics by gender for blood pressure status, antihypertensive drug treatment, urinary albumin excretion (nontransformed and logarithm transformed), microalbuminuria, and creatinine clearance are shown in Table 1. Other variables and descriptive statistics in the present cohort have been previously reported [13]. Figure 1 shows the prevalence of isolated systolic hypertension by gender and age stratum.

In correlation analyses, significant coefficients ($P < 0.001$) were found between systolic and diastolic pressures (men and women, $r = 0.645$ and 0.704), between systolic and pulse pressures ($r = 0.841$ and 0.860), between systolic and mean pressures ($r = 0.898$ and 0.919), between diastolic and pulse pressures ($r = 0.130$ and 0.242), between diastolic and mean pressures ($r = 0.915$ and 0.927), and between pulse and mean pressures ($r = 0.518$ and 0.588). Findings were similar with the exclusion of those on antihypertensive drug treatment (data not shown).

Relationship of pulse pressure to urinary albumin excretion

Univariate analyses. The relationship of pulse pressure to logarithm-transformed urinary albumin excretion was significantly positive in linear regression analysis. The linear regression coefficient was 0.00184 for men ($P =$

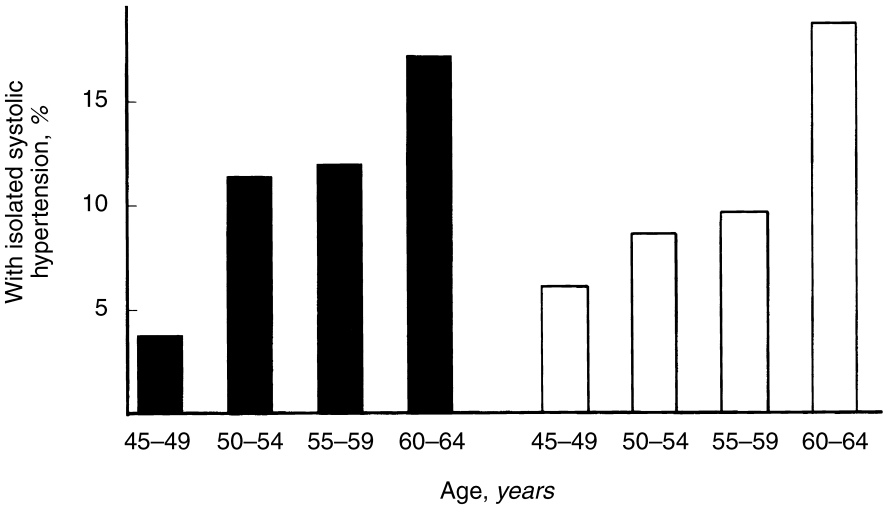

Fig. 1. Percent prevalence of isolated systolic hypertension by age in men (■) and women (□). Isolated systolic hypertension was defined as systolic pressure ≥140 mm Hg in subjects not on treatment with antihypertensive drug(s) and with a diastolic pressure <90 mm Hg. The number of people represented in the age ranges are 103 to 137 men and 145 to 186 women.

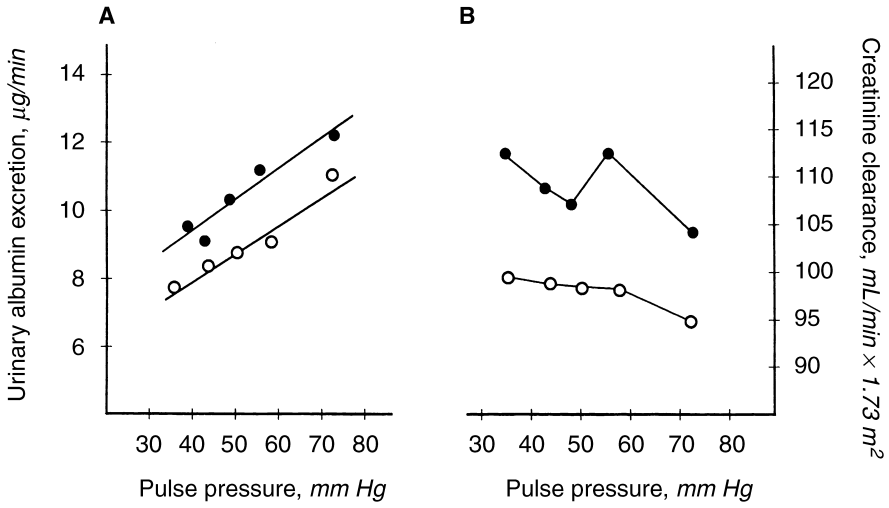

Fig. 2. Mean values of urinary albumin excretion (*A*) and of creatinine clearance (*B*) plotted over the mean of pulse pressure in quintiles of pulse pressure for men (●) and women (○). *P* values are given by a test for linearity across quintiles (ANOVA). In panel A, $P = 0.007$ for men and $P < 0.001$ for women; in panel B, $P = 0.234$ for men and $P = 0.269$ for women. The number of persons per quintile are 131 to 139 men and 173 to 179 women.

0.045) and 0.00286 for women ($P < 0.001$), and the difference between men and women was not significant. In the analysis for men and women controlling for gender, the linear regression coefficient was 0.00240 ($P < 0.001$). Findings were similar when subjects on regular antihypertensive drug treatment were excluded (men and women combined with control for gender, 0.00294, $P < 0.001$) and when those with a diastolic pressure of ≥90 mm Hg were excluded (0.00230, $P < 0.001$). Figure 2 shows the mean values of urinary albumin excretion and of creatinine clearance plotted over the mean of pulse pressure in quintiles of pulse pressure values. Pulse pressure was linearly related to urinary albumin excretion in both sexes, that is, the slope of the line was similar in men and women. No significant association was found between pulse pressure and creatinine clearance. These findings were similar when those on antihypertensive drug treatment were excluded (data not shown).

Multivariate analyses. The relationship of pulse pressure to logarithm-transformed urinary albumin excretion was significantly positive in a multivariate model when it was controlled for age, body mass index, logarithm-transformed cigarettes per day, antihypertensive drug treatment, plasma cholesterol, glucose, and creatinine clearance. The multivariate regression coefficient of pulse pressure to logarithm-transformed urinary albumin excretion for men and women combined as well as controlling for gender was 0.00217 ($P < 0.001$). In this multivariate model, coefficients for other variables were similar to our earlier report [13]. The multivariate regression coefficient of pulse pressure to logarithm-transformed urinary albumin excretion also was significantly positive with the exclusion of subjects on antihypertensive drug treatment (0.00262, $P < 0.001$) and excluding those with a diastolic pressure ≥90 mm Hg (0.00187, $P = 0.006$). The multivariate regression coefficient of pulse pressure

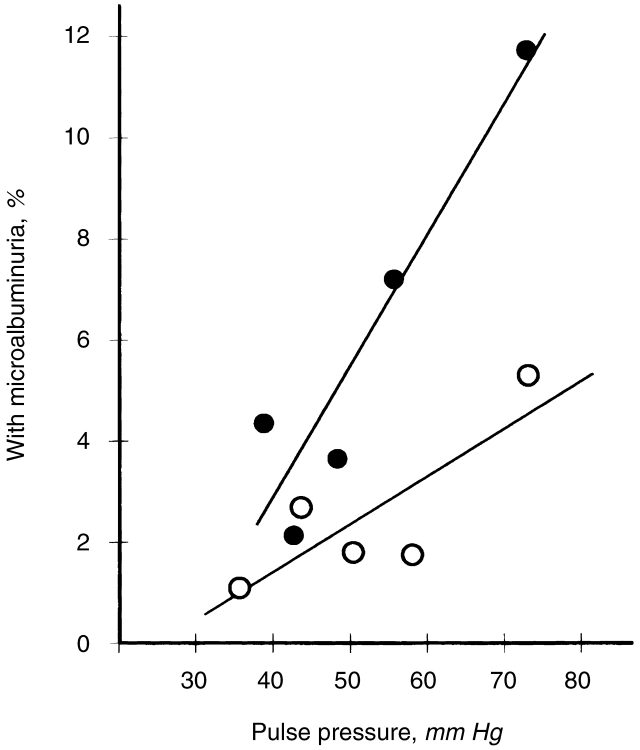

Fig. 3. Percent prevalence of microalbuminuria (urinary albumin excretion 20 to 199 μg/min) plotted over the mean of pulse pressure in quintiles of pulse pressure for men (●) and women (○). $P < 0.001$ for both men and women, by a test for linearity across quintiles (chi-square analysis). The number of persons per quintile are 131 to 139 men and 173 to 179 women.

to logarithm-transformed urinary albumin excretion was significantly positive in an additional model with inclusion of diastolic pressure among independent variables (0.00176, $P = 0.005$). In this additional model, the coefficient of diastolic pressure was significantly positive (0.00354, $P < 0.001$). Systolic pressure and mean pressure were never included in the multivariate analyses together with pulse pressure, since they were high-order correlated with pulse pressure and thus unlike other variables.

To investigate the role of renal function in the relationship between pulse pressure and urinary albumin excretion further, the multivariate linear regression coefficient of pulse pressure to logarithm-transformed urinary albumin excretion was compared between the two subgroups with creatinine clearance values below the median and above the median (men and women, 104.5 and 93.4 mL/min × 1.73 m^2). Mean values of creatinine clearance for the two subgroups were 77.9 and 127.5 mL/min × 1.73 m^2, respectively ($N = 778$ and 779). Controlling for gender and other variables, the multivariate linear regression coefficients of pulse pressure to logarithm-transformed urinary albumin excretion were not significantly different between two subgroups (0.00189 and 0.00233).

Table 2. Multiple logistic regression analysis: Relationship of pulse pressure and other variables[a] to the prevalence of microalbuminuria[b]

Variable	Difference	Relative risk	95% Confidence interval
Pulse pressure	15 mm Hg	1.71[b]	(1.31–2.22)
Plasma cholesterol	1.0 mmol/L	1.94[b]	(1.49–2.52)
Body mass index	4 kg/m^2	1.48[b]	(1.16–1.91)
Logarithm-transformed cigarettes/day	0.5	1.20[a]	(1.01–1.55)
Gender	men/women	2.90[b]	(1.48–4.88)

[a] Also in model: age, use of an antihypertensive drug(s), plasma glucose, and creatinine clearance, not significantly related to microalbuminuria
[b] Defined as urinary albumin excretion 20–199 μg/min
[c] $P < 0.05$; [d] $P < 0.001$

Relationship of pulse pressure to microalbuminuria

Univariate analyses. The relationship of pulse pressure to microalbuminuria was either positive and significant or borderline significant in logistic regression analyses. The logistic regression coefficients were 0.0402 ($P < 0.001$) for men and 0.0220 ($P = 0.098$) for women; the difference between men and women was not significant. In an analysis of men and women combined with a control for gender, the logistic regression coefficient was 0.0343 ($P < 0.001$). Coefficients were similar with exclusion of subjects on regular antihypertensive drug treatment (men and women combined with a control for gender: 0.0387, $P < 0.001$) and with the exclusion of people with a diastolic pressure ≥90 mm Hg (0.0381, $P < 0.001$). Figure 3 shows the prevalence of microalbuminuria plotted over the mean pulse pressure value in quintiles of pulse pressure. In both sexes, there was a significant linear trend for the relationship of pulse pressure and a prevalence of microalbuminuria, but while the slope of the line was higher, it was not significantly different between men and women. Findings were similar when persons on antihypertensive drug treatment were excluded (data not shown).

Multivariate analyses. The relationship of pulse pressure to microalbuminuria was significantly positive in a multivariate model with controls for age, body mass index, logarithm-transformed cigarettes per day, antihypertensive drug treatment, plasma cholesterol, glucose, and creatinine clearance. The multivariate logistic regression coefficient of pulse pressure to microalbuminuria for men and women combined with a control for gender was 0.0356 ($P < 0.001$). Table 2 shows the relative risk and 95% CI calculated with an exponentiation of multivariate logistic coefficients of the pulse pressure values and other significant correlates of microalbuminuria. The multivariate logistic coefficient of pulse pressure to microalbuminuria also was significantly positive in analyses excluding subjects on antihypertensive drug treatment (0.0447, $P < 0.001$) and excluding those with a diastolic pressure ≥90 mm Hg (0.0394, $P < 0.001$).

Table 3. Blood pressure, urinary albumin excretion, and microalbuminuria by blood pressure status: Mean or prevalence in men and women combined with control for gender

		Hypertensives[b]			
		On antihypertensive drug		Not on antihypertensive drug	
	Nonhypertensives[a]	controlled[c]	not controlled[d]	with isolated systolic hypertension[e]	with diastolic pressure ≥90 mmHg
Number of persons *men/women*	414/546	70/76	43/87	75/97	75/84
Systolic pressure *mm Hg*	119.8	126.8	153.2	149.8	150.3
Diastolic pressure *mm Hg*	74.4	78.8	88.0	80.8[h]	94.3
Pulse pressure *mm Hg*	45.4	47.9	65.2	69.0[h]	56.1
Mean pressure *mm Hg*	89.5	94.8	109.7	103.8[h]	113.0
Urinary albumin excretion *μg/min*	8.39	10.44	11.76	12.40[g]	11.03
With microalbuminuria[f] %	1.57	4.64	11.12	6.39[g]	7.77
Creatinine clearance *mL/min* × *1.73 m² BSA*	103.4	101.8	100.9	101.4	103.5

[a] With systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg and not on antihypertensive drug
[b] With systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg and/or on antihypertensive drug
[c] On antihypertensive drug with systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg
[d] On antihypertensive drug with systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg
[e] Not on antihypertensive drug with systolic pressure ≥140 mm Hg and diastolic pressure <90 mm Hg
[f] Urinary albumin excretion 20–199 μg/min
[g] $P < 0.001$ compared to nonhypertensives
[h] $P < 0.001$ compared to untreated hypertensives with diastolic pressure ≥90 mm Hg

The multivariate logistic coefficient of pulse pressure to microalbuminuria was significantly positive in an additional model, with the inclusion of diastolic pressure among the independent variables (0.0295, $P = 0.001$). In this additional model, the coefficient of diastolic pressure was significantly positive (0.0543, $P < 0.001$). Systolic pressure and mean pressure values were never included in multivariate analyses together with pulse pressure, since they were high-order correlated with pulse pressure, unlike other variables.

Relationship of isolated systolic hypertension to urinary albumin excretion and microalbuminuria

Table 3 shows urinary albumin excretion and the prevalence of microalbuminuria by blood pressure status. Untreated hypertensives with isolated systolic hypertension had a greater urinary albumin excretion and prevalence of microalbuminuria compared with nonhypertensives and treated hypertensives with controlled blood pressure. The difference was significant when compared with nonhypertensives. Within the group of untreated hypertensive subjects, persons with isolated systolic hypertension and persons with diastolic pressure ≥90 mm Hg had similar urinary albumin excretion rates and a similar prevalence of microalbuminuria in the presence of significant differences for diastolic, pulse, and mean pressure. Creatinine clearance was not significantly different between nonhypertensives and hypertensives, independent of blood pressure status and of antihypertensive drug treatment. Findings were similar in analyses for men and women separately and with a control for other variables (data not shown).

In the multivariate logistical analysis for men and women combined, with a control for gender, age, body mass index, logarithm-transformed cigarettes per day, plasma cholesterol, glucose, and creatinine clearance, the relative risk of microalbuminuria for untreated hypertensives with isolated systolic hypertension compared with nonhypertensive subjects was 4.95 (95% CI, 3.15 to 7.76). Findings were similar in an additional model with the inclusion of diastolic pressure among the independent variables (relative risk = 5.11, 95% CI, 3.10 to 8.40).

DISCUSSION

This study reports the novel finding that in a population sample of nondiabetic, middle-aged men and women, pulse pressure and isolated systolic hypertension are directly related to microalbuminuria, independent of several other correlates. These findings were consistent with the use of urinary albumin excretion, indicating that the relationship was not limited to the high range of urinary albumin excretion. In both sexes, the relationships of pulse pressure to urinary albumin excretion and microalbuminuria were linear over the range of pulse pressures, and were significant not only from a statistical viewpoint. The risk of microalbuminuria differed by about 70% for a difference of one standard deviation in pulse pressure and of about five times in the presence of isolated systolic hypertension. Findings were not significantly different between sexes. However, men tended to have a higher slope than women for the relationship between pulse pressure and microalbuminuria, in contrast to both genders having a similar slope for the relationship between pulse pressure and urinary albumin excretion. This contrast indicated the existence of few "outliers," that is,

men with high pulse pressure and microalbuminuria values or women with high pulse pressure and no microalbuminuria. These few cases could not influence data on urinary albumin excretion because of their low relative weight in statistical analyses, and they were apparent only in analyses focused on the low percentage of individuals with microalbuminuria. Theoretically, they could reflect a limited precision of curve fitting for microalbuminuria or a subgroup with a real difference in the relationship between pulse pressure and microalbuminuria. For being gender associated, this difference could be explained by genetic and/or environmental factors that may be differently prevalent in the two sexes.

The use of a single measure of urinary albumin, blood pressure and other variables likely resulted in a limited precision of the classification of individuals, and thus in a regression dilution bias. Antihypertensive treatment might have attenuated the strength of the relationships; in fact, coefficients of pulse pressure tended to be higher in the analyses without the inclusion of treated hypertensive subjects than for the entire cohort. For gender, smoking, plasma cholesterol, and body mass index, the present data show that the associations of these factors with microalbuminuria are also independent of pulse pressure. Moreover, the study reports the novel observation that creatinine clearance, used as an index of glomerular filtration, was not related to pulse pressure, nor was it altered in the presence of isolated systolic hypertension.

A cross sectional relationship of blood pressure to urinary albumin excretion could reflect several mechanisms, not necessarily alternative. An influence of urinary albumin excretion on pulse pressure mediated via renal dysfunction seems unlikely. Findings for pulse pressure were statistically independent of creatinine clearance and were similar in the two subgroups, with a difference in creatinine clearance of about 50 mL/min. An influence of pulse pressure on urinary albumin excretion appears to be a reasonable pathogenic mechanism, since systemic blood pressure affects the escape of albumin from the renal glomerulus unless a preglomerular vasoconstriction protects the glomerular filter. Studies of renal hemodynamics in isolated systolic hypertension are not available. In clinically defined hypertension and in persons at risk of hypertension, renal hemodynamics are characterized by a postglomerular vasoconstriction, which maintains glomerular filtration in the normal range despite a low renal blood flow [28, 29]. If such a hemodynamic pattern was also present in isolated systolic hypertension, as suggested by present data for creatinine clearance, the influence of high systemic pressure on the glomerulus could favor the onset of microalbuminuria. Other possible mechanisms—such as a "third" unidentified factor or group of factors driving pulse pressure and urinary albumin excretion—could not be investigated by the present study and remain speculative.

The present data might also have practical implications. Several epidemiological and clinical studies report that high pulse pressure and isolated systolic hypertension are associated with signs of target organ damage and cardiovascular disease in the presence of low-normal diastolic pressure [30–37]. The present study shows that this is also true for the kidney. In fact, nondiabetic persons with isolated systolic hypertension had urinary albumin excretion rates and a prevalence of microalbuminuria as high as the untreated hypertensive subjects with diastolic pressure values $\geq$90 mm Hg, despite lower values of diastolic pressure and mean pressure. Thus, nondiabetic persons with isolated systolic hypertension are at a high risk of microalbuminuria, which is considered to be the renal manifestation of vascular disease [5]. The data support the concept that to prevent, to delay, and to control the vascular damage, microalbuminuria should be searched for in persons with a moderate elevation in systolic pressure isolated from a parallel increase in diastolic pressure. The data should be extrapolated cautiously to other populations with a different age and ethnicity. The possibility that microalbuminuria in nondiabetics also could be a risk factor for renal failure is only speculative at present. However, the cross sectional association between isolated systolic hypertension and signs of early glomerular damage is in keeping with the longitudinal association between isolated systolic hypertension and the long-term incidence of end-stage renal disease. Altogether these different observations further support the idea that systolic hypertension must be corrected to slow the progression of renal damage from the early to ultimate stages [38–40].

In summary, our study reports the novel finding of a relationship of pulse pressure to urinary albumin excretion and microalbuminuria, independent of diastolic pressure and other traits related to these variables. On the basis of the present findings, the old belief of focusing attention on diastolic pressure more than on systolic pressure should be considered incorrect in terms of it providing renal protection from microalbuminuria secondary to blood pressure elevation. The simple evaluation of diastolic pressure may indeed underestimate the renal impairment secondary to changes in systemic blood pressure.

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